P-111

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 395 328 A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 90304312.3

(22) Date of filing: 23.04.90

(51) Int. Cl.5: C07D 239/36, C07D 239/54, C07D 239/46, C07D 403/04, A61K 31/505

(30) Priority: 26.04.89 GB 8909560

(43) Date of publication of application: 31.10.90 Bulletin 90/44

(84) Designated Contracting States: AT BE CH DE DK ES FR GB GR IT LI LU NL SE

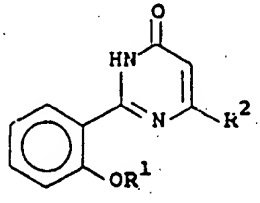
(71) Applicant: SMITH KLINE & FRENCH LABORATORIES LIMITED
Mundells
Welwyn Garden City Hertfordshire, AL7 1EY(GB)

(72) Inventor: Coates, William John
Smith Kline & French Research Limited, The Frythe
Welwyn, Hertfordshire AL6 9AR(GB)
Inventor: Rawlings, Derek Anthony
Smith Kline & French Research Limited, The Frythe
Welwyn, Hertfordshire AL6 9AR(GB)

(74) Representative: Waters, David Martin, Dr. et al
Corporate Patents, Smithkline Beecham,2 Mundells
Welwyn Garden City Hertfordshire AL7 1EY(GB)

(54) **Chemical compounds.**

(57) Compounds of the formula (1) :



(1)

and pharmaceutically acceptable salts thereof are described wherein R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and R^2 is C_{1-6}alkyl, phenyl, hydroxy, C_{1-6}alkoxy, halo, $-NHCOR^3$, $-NHCONHR^4$, 5-tetrazolyl, $-CO_2R^5$, cyano, $-CONR^6R^7$, or $-NR^8R^9$ wherein R^3 to R^7 are independently hydrogen or C_{1-6}alkyl and R^8 and R^9 are independently hydrogen or C_{1-6}alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy.

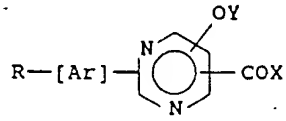
Processes for their preparation, pharmaceutical compositions comprising them and their use as medicaments are also described.

EP 0 395 328 A2

CHEMICAL COMPOUNDS

The present invention relates to phenylpyrimidone derivatives, processes for their preparation, their use as therapeutic agents and to pharmaceutical compositions containing them. The compounds of this invention are inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase and are of use in combatting such conditions where such inhibition is thought to be beneficial. They are bronchodilators and are therefore of use in combatting chronic reversible obstructive lung diseases such as asthma and bronchitis. Furthermore they are vasodilators and are therefore of value in combatting angina, hypertension and congestive heart failure. They are of use in the treatment of gastrointestinal motility disorders, for example irritable bowel syndrome.

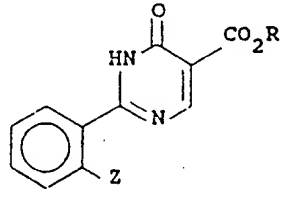
US Patents 3660403 and 3745161 disclose compounds of the general formula (A) :



(A)

wherein COX and OY are ortho to each other and [Ar] is para to either COX or OY, R is inter alia lower alkoxy, [Ar] is inter alia phenyl, X is inter alia hydroxy, amino, alkylamino, dialkylamino or alkoxy, and Y is inter alia hydrogen. These compounds are described as having anti-inflammatory, anti-pyretic and analgesic activity. None of the compounds of the present invention are specifically disclosed.

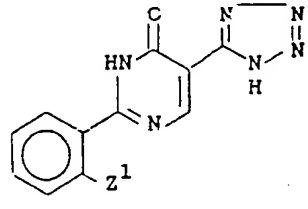
US Patent 4031093 discloses anti-allergic compounds of the formula (B) :



(B)

wherein Z is inter alia C_{2-6}alkoxy or C_{2-6}alkenyloxy and R is hydrogen or the residue of an easily cleavable ester group.

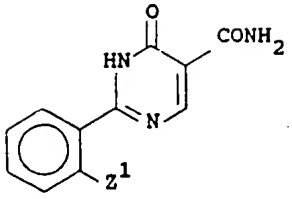
US Patent 4082751 discloses anti-allergic compounds of the formula (C) :



(C)

wherein Z' is inter alia lower alkoxy or lower alkenyloxy.

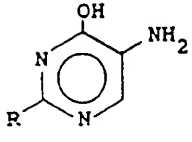
US Patent 4082751 also discloses intermediate compounds of the formula (D) :



(D)

wherein Z^1 is as hereinbefore defined. In J. Med. Chem. 1982, 25, 1145-1150 it is indicated at page 1148 that the compounds of the formula (D) have insignificant anti-allergic activity.

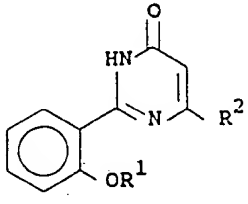
US Patent 4241056 discloses 3-(4-hydroxy-5-pyrimidyl)ureido-penicillins. As intermediates for such compounds are described compounds of the general formula (E) :



(E)

wherein R is inter alia phenyl optionally substituted by C_{1-6}alkoxy. None of the compounds of the present invention are specifically disclosed.

According to the present invention there is provided compounds of the formula (1) :



(1)

and pharmaceutically acceptable salts thereof, wherein

R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and

R^2 is C_{1-6}alkyl, phenyl, hydroxy, C_{1-6}alkoxy, halo, -NHCOR^3, -NHCONHR^4, 5-tetrazolyl, -CO_2R^5, cyano, -CONR^{6}R^7, or -NR^{8}R^9 wherein R^3 to R^7 are independently hydrogen or C_{1-6}alkyl and R^8 and R^9 are independently hydrogen or C_{1-6}alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy.

Suitably R^1 is C_{2-5}alkyl for example ethyl, n-propyl, isopropyl, butyl, isobutyl or pentyl.

Suitably R^1 is C_{3-5}alkenyl for example allyl, butenyl or pentenyl.

Suitably R^1 is cyclopropylmethyl or benzyl.

Examples of C_{1-6}alkyl substituted by 1 to 6 fluoro groups include -CF_3, -CH_2CF_3 or -CF_2CHFCF_3.

Preferably R^1 is n-propyl.

Suitably R^2 is phenyl or C_{1-6}alkyl for example methyl, ethyl, propyl or butyl.

Suitably R^2 is hydroxy, C_{1-6}alkoxy for example methoxy, ethoxy or propoxy, or halo for example fluoro, chloro, bromo or iodo.

Suitably R^2 is -NHCOR^3 for example formamido, acetamido, propionamido or butyramido.

Suitably R^2 is -NHCONHR^4 for example ureido or N-methylureido.

Suitably R^2 is 5-tetrazolyl or -CO_2R^5 for example carboxy, methoxycarbonyl or ethoxycarbonyl.

Suitably R^2 is -cyano or -CONR^{6}R^7 for example carboxamido, N-methylcarboxamido, N-ethylcarboxamido or N-propylcarboxamido.

Suitably R^2 is -NR^{8}R^9 for example amino, methylamino, ethylamino, propylamino, 2-hydroxyethylamino,

3-hydroxypropylamino or bis-(2-hydroxyethyl)amino.

Specific compounds of this invention are :

6-amino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-acetamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propionamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-butyramido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-N'-methylureido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4,6-dihydroxy-2-(2-propoxyphenyl)pyrimidine,
4-chloro-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
6-ethylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(2-hydroxyethylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(3-hydroxypropylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4-hydroxy-6-methyl-2-(2-propoxyphenyl)pyrimidine,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylic acid,
ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylate,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
4-cyano-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
2-(2-propoxyphenyl)-6-(1H-tetrazol-5-yl)pyrimidin-4(3H)-one,
4-ethyl-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
4-hydroxy-6-phenyl-2-(2-propoxyphenyl)pyrimidine,
N-methyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-propyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
6-ethoxy-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
6-N,N-bis-(2-hydroxyethyl)amino-2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or pharmaceutically acceptable salts thereof.

This invention covers all tautomeric and optical isomeric forms of compounds of formula (1).

Compounds of the formula (1) wherein R^2 is $-NR^8R^9$ may form pharmaceutically acceptable salts with acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acids.

Compounds of the formula (1) may form pharmaceutically acceptable salts with metal ions, such as alkali metals for example sodium and potassium, or with an ammonium ion.

In order to use a compound of the formula (1) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of formula (1) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, sub-lingually, parenterally, transdermally, rectally, via inhalation or via buccal administration.

Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, starch, celluloses, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil or solubilising agent, for example polyethylene glycol, polyvinylpyrrolidone, 2-pyrrolidone, cyclodextrin, lecithin, arachis oil, or sesame oil.

A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

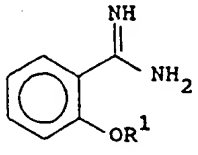
Each dosage unit for oral administration contains suitably from 0.001 mg/Kg to 30 mg/Kg, and preferably from 0.005 mg/Kg to 15 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 10 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for oral administration is suitably about 0.001 mg/Kg to 120 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.005 mg/Kg to 10 mg/Kg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered as required for example from 1 to 8 times a day or by infusion. The compositions of the invention are bronchodilators and are useful in chronic reversible obstructive lung disease for example asthma and bronchitis. The compositions of the present invention are of use in the treatment of gastrointestinal motility disorders, such as irritable bowel syndrome. The compositions of the present invention have vasodilator activity and are of use in the treatment of angina, hypertension and congestive heart failure. Such conditions can be treated by administration orally, sub-lingually, topically, rectally, parenterally or by inhalation. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1-5.0 mg of a compound of the formula (1) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active compound or compounds are formulated in a pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are bronchodilators such as sympathomimetic amines for example isoprenaline, isoetharine, sulbutamol, phenylephrine and ephedrine or xanthine derivatives for example theophylline and aminophylline, anti-allergic agents for example disodium cromoglycate, histamine H_1-antagonists, vasodilators for example hydralazine, angiotensin converting enzyme inhibitors for example captopril, anti-anginal agents for example isosorbide nitrate, glyceryl trinitrate and pentaerythritol tetranitrate, anti-arrhythmic agents for example quinidine, procainamide and lignocaine, calcium antagonists for example verapamil and nifedipine, diuretics such as thiazides and related compounds for example bendrofluazide, chlorothiazide, chlorothalidone, hydrochlorothiazide, and other diuretics for example frusemide and triamterene, and sedatives for example nitrazepam, flurazepam and diazepam.

In another aspect the present invention provides a process for the preparation of compounds of the formula (1) or pharmaceutically acceptable salts thereof, which process comprises :

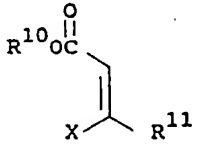
a) for compounds wherein R^2 is amino, reacting a compound of the formula (2) :



(2)

wherein R^1 is as hereinbefore defined with a C_{1-6}alkyl cyanoacetate;

b) for compounds wherein R^2 is hydroxy, phenyl, C_{1-6}alkyl or carboxy, reacting a compound of the formula (2) as hereinbefore defined with a compound of the formula (3) :



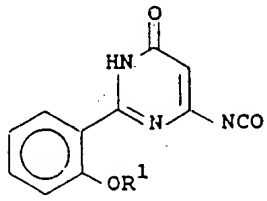
(3)

wherein X is a displaceable group, R^{11} is hydroxy, phenyl, C_{1-6}alkyl or carboxy and R^{10} is an ester forming group;

c) for compounds wherein R^2 is -NHCOR^3, reacting a compound of the formula (1) wherein R^2 is amino with a formylating agent or a C_{2-7}alkanoylating agent;

d) for compounds wherein R^2 is -NHCONHR^4 in which R^4 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is amino with a C_{1-6}alkyl isocyanate;

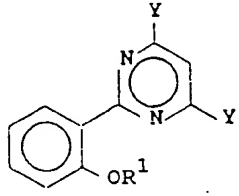
e) for compounds wherein R^2 is -NHCONH$_2$, reacting a compound of the formula (4)



(4)

wherein R^1 is as hereinbefore defined with ammonia;

f) for compounds wherein R^2 is halo, hydrolysing a compound of the formula (5) :



(5)

wherein R^1 is as hereinbefore defined and Y is halo;

g) for compounds wherein R^2 is -NR^{8}R^9, reacting a compound of the formula (1) wherein R^2 is halo with an amine HNR^{8}R^9 wherein R^8 and R^9 are as hereinbefore defined;

h) for compounds wherein R^2 is -CO$_2$R^5 in which R^5 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is carboxy with R^{5}OH in which R^5 is C_{1-6}alkyl in the presence of an acid catalyst;

i) for compounds wherein R^2 is -CONR^{6}R^7, reacting a compound of the formula (1) wherein R^2 is -CO$_2$R^5 in which R^5 is C_{1-6}alkyl with an amine HNR^{6}R^7 wherein R^6 and R^7 are as hereinbefore defined;

j) for compounds wherein R^2 is cyano, dehydrating a compound of the formula (1) wherein R^2 is -CONH$_2$;

k) for compounds wherein R^2 is 5-tetrazolyl, reacting a compound of the formula (1) wherein R^2 is cyano with an azide salt; or

l) for compounds wherein R^2 is C_{1-6}alkoxy, reacting a compound of the formula (1) wherein R^2 is halo with a C_{1-6}alkoxide salt; and thereafter optionally forming a pharmaceutically acceptable salt.

Suitably a compound of the formula (2) is treated with a C_{1-6}alkyl cyanoacetate such as ethyl cyanoacetate or a compound of the formula (3) in water or an organic solvent such as a C_{1-4}alkanol or dimethylformamide or mixtures thereof in the presence of a base such as sodium hydroxide, a sodium alkoxide or sodium hydride at ambient or elevated temperature, for example 40-150° C, conveniently at the reflux temperature of the reaction mixture.

Suitably X is hydroxy or a derivative thereof, for example X is protected hydroxy such as silyloxy, an acid residue (for example C_{1-6}alkanoyloxy) or an ether residue (for example methoxy or ethoxy). Suitably R^{10} is C_{1-6}alkyl, for example methyl or ethyl. Preferably when R^{11} is hydroxy, R^{10} is ethyl and X is ethoxy, that is a compound of the formula (2) is reacted with diethylmalonate. Preferably when R^{11} is methyl, ethyl or phenyl, R^{10} is ethyl and X is hydroxy, that is a compound of the formula (2) is reacted with ethyl acetoacetate, ethyl propionylacetate or ethyl benzoylacetate. Preferably when R^{11} is carboxy, R^{10} is ethyl and X is hydroxy, that is a compound of the formula (2) is reacted with ethyl 4-oxalacetate.

The reaction between a compound of the formula (1) wherein R^2 is amino and a formylating agent or a

C_{2-7}alkanoylating agent is conveniently performed in the absence of a solvent or in a suitable solvent such as a N-methylpyrrolidone or pyridine at ambient or elevated temperature, for example 50-200°C, preferably 100-150°C. Examples of formylating agents include formic acid, C_{1-4}alkyl formate or C_{1-4}alkyl formamide. Examples of C_{2-7}alkanoylating agents include acid anhydrides such as acetic, propionic, or n-butyric anhydride or acid halides such as acetyl or propionyl chloride.

The reaction between a compound of the formula (1) wherein R^2 is amino and a C_{1-6}alkyl isocyanate or the reaction between a compound of formula (4) and ammonia is conveniently performed in an organic solvent such as dioxan, toluene or a halohydrocarbon such as chloroform at ambient or elevated temperature, for example 50-150°C, preferably at the reflux temperature of the reaction mixture.

A compound of the formula (5) is suitably hydrolysed by reaction with a concentrated acid such as hydrochloric acid in an organic solvent such as a C_{1-4}alkanol. Suitably Y is chloro or bromo.

The reaction between a compound of the formula (1) wherein R^2 is halo and an amine HNR^8R^9 is suitably performed in an organic solvent such as a C_{1-4}alkanol at an elevated temperature, for example 50-120°C, conveniently in a pressure vessel.

A compound of the formula (1) wherein R^2 is carboxy is suitably reacted with an excess of R^5OH in the absence of a solvent or in the presence of an inert solvent such as toluene or a halohydrocarbon, at an elevated temperature, for example 40-120°C, preferably at the reflux temperature of the reaction mixture. A suitable acid catalyst is concentrated sulphuric acid or anhydrous hydrogen chloride.

The reaction of a compound of the formula (1) wherein R^2 is CO_2R^5 in which R^5 is C_{1-6}alkyl with HNR^6R^7 is suitably performed in water or an organic solvent such as a C_{1-4}alkanol or mixtures thereof at ambient or elevated temperature, for example 40-120°C, conveniently at the reflux temperature of the reaction mixture.

A compound of the formula (1) wherein R^2 is $-CONH_2$ is suitably reacted with a dehydrating agent such as phosphorous pentoxide, phosphoryl chloride or thionyl chloride in the absence of a solvent or in an inert organic solvent such as toluene at ambient or elevated temperature, for example 40-120°C, preferably at the reflux temperature of the reaction mixture. The reaction with phosphoryl chloride may result in the formation of an intermediate chloropyrimidine compound which is suitably hydrolysed to the desired pyrimidone by reaction with glacial acetic acid at elevated temperature, for example 40-120°C.

The reaction of a compound of the formula (1) wherein R^2 is cyano with an azide salt is suitably performed in an organic solvent such as dimethylformamide, dimethylsulfoxide, N-methylpyrrolidine-2-one or tetrahydrofuran at an elevated temperature, for example 40-200°C, preferably at the reflux temperature of the reaction mixture. Suitable azide salts include ammonium, sodium, potassium or aluminium azide.

A compound of the formula (1) wherein R^2 is halo is suitably reacted with a C_{1-6}alkoxide salt, such as an alkali metal C_{1-6}alkoxide for example sodium ethoxide or sodium methoxide in an organic solvent such as a C_{1-4}alkanol at an elevated temperature, for example 50-140°C, conveniently in a pressure vessel.

A compound of the formula (4) is suitably prepared by reacting a compound of the formula (1) wherein R^2 is amino with phosgene or a chemical equivalent thereof. Chemical equivalents of phosgene include trichloromethyl chloroformate or carbonyldiimidazole.

A compound of the formula (5) is conveniently prepared by reaction of a compound of the formula (1) wherein R^2 is hydroxy with a halogenating agent such as phosphoryl chloride, thionyl chloride or phosphorous tribromide. Alternatively a compound of the formula (1) wherein R^2 is hydroxy is converted to a tosyl derivative which is then reacted in conventional manner with a halide anion, such as fluoride, chloride, bromide or iodide to form a compound of the formula (5).

Compounds of the formula (2) are known or preparable in conventional manner from US Patent 3,819,631.

Pharmaceutically acceptable acid addition salts of the compounds of the formula (1) wherein R^2 is $-NR^8R^9$ may be prepared from the corresponding base of the compounds of the formula (1) in conventional manner. For example the base may be reacted with an acid in a C_{1-4}alkanol, or an ion-exchange resin may be used. The salts of the compounds of the formula (1) may be interconverted using ion-exchange resins. Non-pharmaceutically acceptable salts are therefore of use as they can be converted to pharmaceutically acceptable salts.

Pharmaceutically acceptable base addition salts of the compounds of the formula (1) may be prepared by standard methods, for example by reacting a solution of the compound of the formula (1) with a solution of the base.

The following biological test methods, data and Examples serve to illustrate this invention.

Bronchodilatation - In vivo

Male guinea-pigs of the Dunkin Hartley strain (500 - 600g) were anaesthetised with Sagatal (pentobarbital sodium) (60 mg/kg). Airway resistance was measured using a modification of the classical Konzett-Rossler technique (J. Pharm. Methods, 13, 309-315, 1985). U46619 (9,11-methanoepoxy-PGH_2) was infused i.v. at a rate of 2.5 nmol/min, this produced a steady state of bronchoconstriction (approximately 120% increase from basal airway resistance). The compound under test was administered by i.v. bolus injection, and the subsequent peak inhibition of bronchoconstriction recorded.

The dose of compound required to reduce the U46619 -induced bronchoconstriction by 50% is given as the BD_{50}. These results demonstrate in vivo anti-bronchoconstrictor activity.

COMPOUND	BD_{50} (µmol/kg)
5	8.34
16	6.03
18	9.70

Phosphodiesterase activity

The activity of the compounds of the present invention as inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase was measured using the procedure described in European Patent Application No. 293063. The compounds of Examples 1 to 24 had IC_{50} values (the concentration of inhibitor required for 50% inhibition of enzyme activity) in the range 0.5 to 88 µM. The compounds of the present invention have the advantage that they are selective in not inhibiting cyclic AMP phosphodiesterase (type III).

Inhibition of spontaneous colonic activity - in vitro

Male albino guinea-pigs (300 - 400g) were killed by a blow to the back of the head and exsanguinated. A 2cm long segment of the proximal part of the hypogastric loop of the distal colon was rapidly dissected out and placed in oxygenated (95% O_2, 5% CO_2) modified warm Krebs solution. The tissue was cleaned out with Krebs and the adjoining mesentery discarded. Cotton was then tied to each end and the colon was attached to a tissue holder in an organ bath containing modified oxygenated Krebs solution at 37°C. The other end of the tissue was tied to an isometric transducer and placed under 1g tension. Force developed by the muscle was detected by the transducer, and recorded on a multitrace pen recorder. Spontaneous colonic activity, as assessed by the contraction distance over a five minute period, was subjected to computer analysis.

The tissues were allowed to settle at a resting tension of 1g for 1 hour, during which time they were washed at 15 minute intervals. Three samples of pre-dose activity were taken and averaged. The tissues were then dosed and two samples of post-dose activity were taken. The lowest value was used to calculate the percentage relaxation, and log dose response curves were constructed. The tissues were washed 10 minutes after dosing and left for 15 minutes to settle prior to the next control period.

The concentration of compound required to reduce spontaneous colonic activity by 50% is given as the IC_{50}.

COMPOUND	IC_{50} (µM)
5	2.4
15	0.75
18	3.3
21	3.7

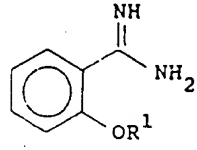
N-propyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
6-ethoxy-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
6-N,N-bis-(2-hydroxyethyl)amino-2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

12. A compound according to any one of claims 1 to 11 for use as a medicament.

13. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 11 and a pharmaceutically acceptable carrier.

14. A process for preparing a compound of the formula (1) or a pharmaceutically acceptable salt thereof as defined in claim 1 which process comprises:

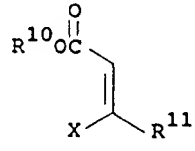
a) for compounds wherein R^2 is amino, reacting a compound of the formula (2) :



(2)

wherein R^1 is as defined in claim 1 with a C_{1-6}alkyl cyanoacetate;

b) for compounds wherein R^2 is hydroxy, phenyl, C_{1-6}alkyl or carboxy, reacting a compound of the formula (2) as hereinbefore defined with a compound of the formula (3) :



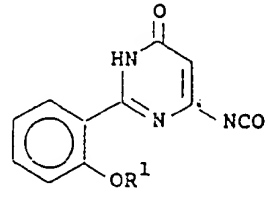
(3)

wherein X is a displaceable group, R^{11} is hydroxy, phenyl, C_{1-6}alkyl or carboxy and R^{10} is an ester forming group;

c) for compounds wherein R^2 is -NHCOR^3, reacting a compound of the formula (1) wherein R^2 is amino with a formylating agent or a C_{2-7}alkanoylating agent;

d) for compounds wherein R^2 is -NHCONHR^4 in which R^4 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is amino with a C_{1-6}alkyl isocyanate;

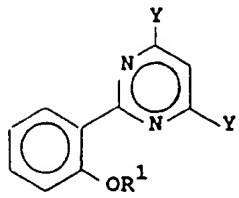
e) for compounds wherein R^2 is -NHCONH$_2$, reacting a compound of the formula (4)



(4)

wherein R^1 is as hereinbefore defined with ammonia;

f) for compounds wherein R^2 is halo, hydrolysing a compound of the formula (5) :

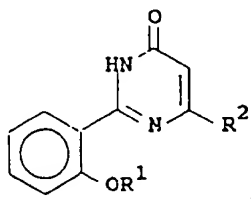


(5)

wherein R^1 is as hereinbefore defined and Y is halo;
g) for compounds wherein R^2 is $-NR^8R^9$, reacting a compound of the formula (1) wherein R^2 is halo with an amine HNR^8R^9 wherein R^8 and R^9 are as defined in claim 1;
h) for compounds wherein R^2 is $-CO_2R^5$ in which R^5 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is carboxy with R^5CH in which R^5 is C_{1-6}alkyl in the presence of an acid catalyst;
i) for compounds wherein R^2 is $-CONR^6R^7$, reacting a compound of the formula (1) wherein R^2 is $-CO_2R^5$ in which R^5 is C_{1-6}alkyl with an amine HNR^6R^7 wherein R^6 and R^7 are as defined in claim 1;
j) for compounds wherein R^2 is cyano, dehydrating a compound of the formula (1) wherein R^2 is $-CONH_2$;
k) for compounds wherein R^2 is 5-tetrazolyl, reacting a compound of the formula (1) wherein R^2 is cyano with an azide salt; or
l) for compounds wherein R^2 is C_{1-6}alkoxy, reacting a compound of the formula (1) wherein R^2 is halo with a C_{1-6}alkoxide salt;
and thereafter optionally forming a pharmaceutically acceptable salt.

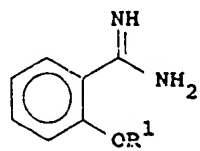
Claims for the following Contracting States: ES, GR

1. A process for preparing a compound of the formula (1) :



(1)

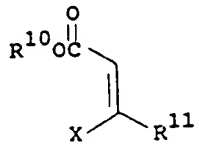
or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and
R^2 is C_{1-6}alkyl, phenyl, hydroxy, C_{1-6}alkoxy, halo, $-NHCOR^3$, $-NHCONHR^4$, 5-tetrazolyl, $-CO_2R^5$, cyano, $-CONR^6R^7$, or $-NR^8R^9$ wherein R^3 to R^7 are independently hydrogen or C_{1-6}alkyl and R^8 and R^9 are independently hydrogen or C_{1-6}alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy;
which process comprises :
a) for compounds wherein R^2 is amino, reacting a compound of the formula (2) :



(2)

wherein R^1 is as hereinbefore defined in claim 1 with a C_{1-6}alkyl cyanoacetate;

b) for compounds wherein R^2 is hydroxy, phenyl, C_{1-6}alkyl or carboxy, reacting a compound of the formula (2) as hereinbefore defined with a compound of the formula (3) :



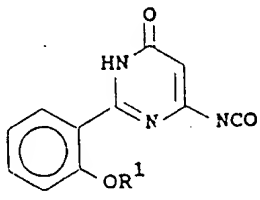
(3)

wherein X is a displaceable group, R^{11} is hydroxy, phenyl, C_{1-6}alkyl or carboxy and R^{10} is an ester forming group;

c) for compounds wherein R^2 is -NHCOR^3, reacting a compound of the formula (1) wherein R^2 is amino with a formylating agent or a C_{2-7}alkanoylating agent;

d) for compounds wherein R^2 is -NHCONHR^4 in which R^4 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is amino with a C_{1-6}alkyl isocyanate;

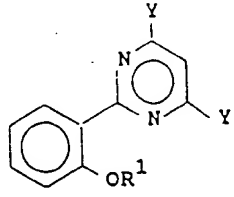
e) for compounds wherein R^2 is -NHCONH$_2$, reacting a compound of the formula (4)



(4)

wherein R^1 is as hereinbefore defined with ammonia;

f) for compounds wherein R^2 is halo, hydrolysing a compound of the formula (5) :



(5)

wherein R^1 is as hereinbefore defined and Y is halo;

g) for compounds wherein R^2 is -NR^{8}R^9, reacting a compound of the formula (1) wherein R^2 is halo with an amine HNR^{8}R^9 wherein R^8 and R^9 are as hereinbefore defined in claim 1;

h) for compounds wherein R^2 is -CO$_2$R^5 in which R^5 is C_{1-6}alkyl, reacting a compound of the formula (1) wherein R^2 is carboxy with R^{5}OH in which R^5 is C_{1-6}alkyl in the presence of an acid catalyst;

i) for compounds wherein R^2 is -CONR^{6}R^7, reacting a compound of the formula (1) wherein R^2 is -CO$_2$R^5 in which R^5 is C_{1-6}alkyl with an amine HNR^{6}R^7 wherein R^6 and R^7 are as hereinbefore defined in claim 1;

j) for compounds wherein R^2 is cyano, dehydrating a compound of the formula (1) wherein R^2 is -CONH$_2$;

k) for compounds wherein R^2 is 5-tetrazolyl, reacting a compound of the formula (1) wherein R^2 is cyano, with an azide salt; or

l) for compounds wherein R^2 is C_{1-6}alkoxy, reacting a compound of the formula (1) wherein R^2 is halo with a C_{1-6}alkoxide salt;

and thereafter optionally forming a pharmaceutically acceptable salt.

2. A process according to claim 1 wherein R^1 is C_{2-5}alkyl.

3. A process according to claim 1 wherein R^1 is C_{3-5}alkenyl.

4. A process according to claim 1 wherein R^1 is n-propyl.

5. A process according to any one of claims 1 to 4 wherein R^2 is phenyl or C_{1-6}alkyl.

6. A process according to any one of claims 1 to 4 wherein R^2 is hydroxy, C_{1-6}alkoxy or halo.

7. A process according to any one of claims 1 to 4 wherein R^2 is -NHCOR^3 or -NHCONHR^4.

8. A process according to any one of claims 1 to 4 wherein R^2 is 5-tetrazolyl or -CO_2R^5.

9. A process according to any one of claims 1 to 4 wherein R^2 is cyano or -CONR^{6}R^7.

10. A process according to any one of claims 1 to 4 wherein R^2 is -NR^{8}R^9.

11. A process according to claim 1 for preparing a compound which is :

6-amino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-acetamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propionamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-butyramido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-N'-methylureido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4,6-dihydroxy-2-(2-propoxyphenyl)pyrimidine,
4-chloro-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
6-ethylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(2-hydroxyethylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(3-hydroxypropylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4-hydroxy-6-methyl-2-(2-propoxyphenyl)pyrimidine,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylic acid,
ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylate,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
4-cyano-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
2-(2-propoxyphenyl)-6-(1H-tetrazol-5-yl)pyrimidin-4(3H)-one,
4-ethyl-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
4-hydroxy-6-phenyl-2-(2-propoxyphenyl)pyrimidine,
N-methyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-propyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
6-ethoxy-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
6-N,N-bis-(2-hydroxyethyl)amino-2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

12. A process for preparing a pharmaceutical composition which comprises bringing into association a compound according to any one of claims 1 to 11 and a pharmaceutically acceptable carrier.

[11] 4,209,623

[45] Jun. 24, 1980

United States Patent [19]

Juby

[54] PYRIMIDINE-5-N-(1H-TETRAZOL-5-yl-)-CARBOXAMIDES

[75] Inventor: Peter F. Juby, Jamesville, N.Y.

[73] Assignee: Bristol-Myers Company, New York, N.Y.

[21] Appl. No.: 913,277

[22] Filed: Jun. 7, 1978

[51] Int. Cl.[2] A61K 31/505; C07D 403/12

[52] U.S. Cl. 544/319; 424/251; 546/210; 548/343

[58] Field of Search 544/319

[56] References Cited

U.S. PATENT DOCUMENTS

3,448,107	6/1969	Holland	260/250
3,660,403	5/1972	Shen	260/251 R
3,745,161	7/1973	Snen	260/250 R
3,883,653	5/1975	Barth	424/251
4,031,093	6/1977	Juby	260/251 R
4,082,751	4/1978	Juby	260/256.4 C

OTHER PUBLICATIONS

Ruhemann, S., Ber., 30, 821, (1897).
Mitter et al., "J. Chem. Soc.", 123, 2179, (1923).
Mitter et al., "Quart J. Indian. Chem. Soc.", 2, p. 61, (1925).

Primary Examiner—Donald G. Daus
Assistant Examiner—Lisa Jones
Attorney, Agent, or Firm—David M. Morse

[57] ABSTRACT

A series of 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-N-(1H-tetrazol-5-yl)carboxamides is provided for use as inhibitors of allergic reactions. The compounds show antiallergy activity by both oral and parenteral routes of administration.

27 Claims, No Drawings

PYRIMIDINE-5-N-(1H-TETRAZOL-5-YL)-CARBOXAMIDES

BACKGROUND OF THE INVENTION

1. Field of the Invention:

This invention relates to optionally substituted 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide derivatives and to their use as inhibitors of allergic reactions.

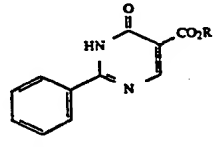
2. Description of the Prior Art:

Various medicinal agents have been employed in the treatment of allergic reactions such as bronchial asthma and allergic rhinitis which are believed to result mainly from antigenantibody interaction. With respect to bronchial asthma, one of the most serious of these allergically-mediated diseases, bronchodilators such as theophylline, isoproterenol, epinephrine and atropine are used primarily in providing symptomatic relief. These agents, however, have undesirable side effects, e.g. cardiac stimulation and gastrointestinal distress.

With the recent introduction of disodium cromoglycate described by J. S. G. Cox, et al. in *Adv. in Drug Res.*, 5, 115–196 (1970), the physician has been provided with an agent which, when administered to asthmatic patients prior to inhalation of specific antigens, inhibits the release of mediators, e.g. histamine and SRS-A (slow-reacting-substance of anaphylaxis), believed to be responsible for the asthmatic response. While making possible a prophylactic treatment for bronchial asthma without cardiovascular side effects and thus representing a significant advance, disodium cromoglycate suffers from a major disadvantage in that it is not orally absorbed and must be administered by inhalation.

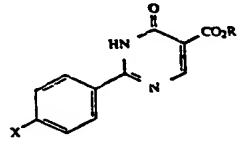
With respect to the compounds of the present invention, no examples of 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-N-(1H-tetrazol-5-yl)carboxamides have been found in the literature. Numerous examples of 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylic acid derivatives are known, however. Illustrative of such compounds are the following:

1. Preparation of the unsubstituted acid and ester of the formula



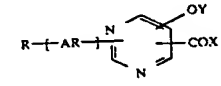
where R is hydrogen or ethyl is disclosed by S. Ruhemann in *Ber.*, 30, 821 (1897).

2. The p-methylphenyl and p-methoxyphenyl substituted esters and acids of the formula



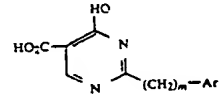
where R is hydrogen or ethyl and X is methyl or methoxy are disclosed by Mitter, et al. in *J. Chem. Soc.*, 123, 2179 (1923) and *Quart. J. Indian Chem. Soc.*, 2, 61 (1925).

3. Shen, et al. in U.S. Pat. Nos. 3,660,403 and 3,745,161 disclose compounds of the general formula



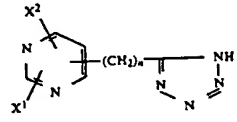
where R–[Ar]– may inter alia be substituted phenyl. Y may be hydrogen and X is any of various substituents including hydroxy, alkoxy or N-heterocyclo. The reference compounds are disclosed as having antiinflammatory, antipyretic and analgesic activity, and no mention is made of any utility as antiallergy agents.

4. U.S. Pat. No. 3,883,653 discloses antiallergy compounds of the formula



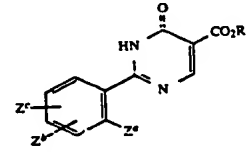
where m is an integer of 0 or 1 and Ar is pyridyl, thienyl, furyl, phenyl or phenyl substituted by hydroxy, methyl, methoxy, nitro, chloro, fluoro, 3,4-dimethoxy, 3,4,5-trimethoxy or alkanoylamino.

5. U.S. Pat. No. 3,448,107 discloses lipid regulating agents of the formula



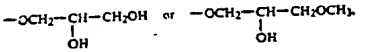
where X^1 and X^2 may be various substituents including hydroxy, phenyl, p-chlorophenyl, p-methylphenyl and p-aminophenyl and n may be 0 to 4.

6. U.S. Pat. No. 4,031,093 discloses 1,6-dihydro-6-oxo-2(ortho-substituted phenyl)pyrimidine-5-carboxylic acid derivatives of the formula



wherein Z^a is —O—C_1—C_8 alkyl, —O—C_2—C_6 alkenyl, —O—$(CH_2)_m$—$CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, —$OCH_2(CH_2)_xO(CH_2)_yCH_3$ in which x and y are each independently either 0 or an integer from

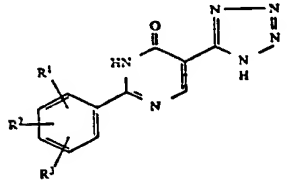
1 to 6, $-OCF_3$, $-OCH_2CF_3$, $-O(CH_2)_uCO_2R^a$ in which u is an integer from 1 to 6 and R^a is hydrogen or C_1–C_6 alkyl, R^c—COO— in which R^c is C_1–C_6 alkyl, —O—CONHR^b in which R^b is C_1–C_6 alkyl, $-O(CH_2)_kOH$ in which k is an integer from 2 to 6,



Z^b has the meaning stated above for Z^a and in addition may be hydrogen, halogen, amino, C_1–C_6 alkylamino, di(C_1–C_6)-alkylamino, $-N(CH_2)_r$ in which r is 4 or 5,

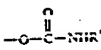
carb(C_1–C_6)alkoxy, C_1–C_6 alkyl, C_2–C_6 alkenyl, CF_3, hydroxy, C_1–C_6 alkylthio, R^c—CO— in which R^c is C_1–C_6 alkyl or R^c—CONH— in which R^c is C_1–C_6 alkyl, Z^c is hydrogen or C_1–C_6 alkoxy and R is hydrogen or the residue of an easily cleavable ester group or a pharmaceutically acceptable salt thereof, provided that when Z^a is methoxy, Z^b and Z^c are not hydrogen and when Z^c is C_1–C_6 alkoxy, Z^a and Z^b are both C_1–C_6 alkoxy.

7. U.S. Pat. No. 4,082,751 discloses 2-phenyl-5-(5-1H-tetrazolyl)pyrimidin-4(3H)-one derivatives of the formula

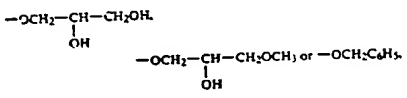


wherein R^1, R^2 and R^3 which may be the same or different are each hydrogen, halogen, (lower)alkyl, (lower)alkenyl, (lower)alkoxy, —O—$(CH_2)_m$—$CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, $-OCH_2(CH_2)_xO(CH_2)_yCH_3$ in which x is 0 or an integer from 1 to 6 and y is 0 or an integer from 1 to 6, CF_3, $-OCF_3$, $-OCH_2CF_3$, hydroxy, (lower)alkylthio, amino, nitro, $-N(CH_2)_r$ in which r is 4 or 5,

(lower)alkylamino, di(lower)alkylamino, carboxyl, $-CO_2$—(lower)alkyl, $-O(CH_2)_uCO_2R^a$ in which u is an integer from 1 to 6 and R^a is hydrogen or (lower)alkyl, acyl, acylamino, acyloxy,



in which R^b is (lower)alkyl, $-O(CH_2)_kOH$ in which k is an integer from 2 to 6,



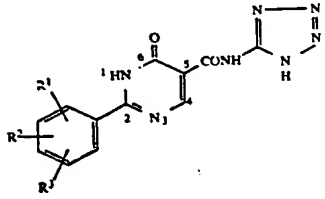
and pharmaceutically acceptable salts thereof, with the proviso that R^1, R^2 and R^3 may not all be alike except in the case where they represent (lower)alkoxy.

SUMMARY OF THE INVENTION

This invention relates to new therapeutically useful 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide derivatives, to processes for their preparation, to pharamaceutical compositions containing them and to methods for treating allergically-mediated diseases in mammals by administration of such derivatives or pharmaceutical compositions.

The compounds of the present invention are useful in the prophylactic treatment of allergic conditions such as bronchial asthma, allergic rhinitis, urticaria, systemic anaphylaxis, conjunctivitis, atopic dermatitis and food allergies. They are of particular value in both reagin-mediated type I hypersensitivity asthma (extrinsic asthma) and the so-called intrinsic asthma in which no sensitivity to any extrinsic antigen can be demonstrated.

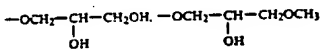
The antiallergy agents of the present invention may be represented by the formula



I

wherein R^1, R^2 and R^3 which may be the same or different are each hydrogen, halogen, (lower)alkyl, (lower)alkenyl, (lower)-alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—$CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, $-OCH_2(CH_2)_xO(CH_2)_yCH_3$ in which x is 0 or an integer from 1 to 6 and y is 0 or an integer from 1 to 6, CF_3, $-OCF_3$, $-OCH_2CF_3$, hydroxy, (lower)alkylthio, amino, nitro, $-N(CH_2)_r$ in which r is 4 or 5, (lower)alkylamino, di(lower)alkylamino, carboxyl, $-CO_2$—(lower)alkyl, $-O(CH_2)_uCO_2R^a$ in which u is an integer from 1 to 6 and R^a is hydrogen or (lower)alkyl, R^c—CO— in which R^c is (lower)alkyl, R^c—CONH— in which R^c is (lower)alkyl, R^c—COO— in which R^c is (lower)alkyl.

in which R^b is (lower)alkyl, $-O(CH_2)_kOH$ in which k is an integer from 2 to 6,



or $-OCH_2C_6H_5$, or a pharmaceutically acceptable salt thereof, with the provisos that (1) no more than two of R^1, R^2 and R^3 are tertiary alkyl or tertiary alkoxy groups, and when two of said R^1, R^2 and R^3 are tertiary alkyl or tertiary alkoxy, they are located on non-adjacent positions and (2) R^1, R^2 and R^3 may not all be alike except in the case where they represent hydrogen or (lower)alkoxy.

DETAILED DESCRIPTION

The R^1, R^2 and R^3 substituents mentioned above may be located at any of the available positions of the phenyl ring, i.e. at the 2–6 positions. The substituents groups may be further defined as follows:

(a) Halogen includes chlorine, bromine, fluorine and iodine;

(b) (Lower)alkyl includes both straight and branched chain saturated aliphatic hydrocarbon radicals having from 1–6 carbon atoms inclusive, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, etc.;

(c) (Lower)alkenyl includes straight or branched unsaturated aliphatic hydrocarbon radicals containing one double bond and having from 2–6 carbon atoms inclusive, e.g. vinyl, allyl, isopropenyl, 2- or 3-methallyl or 3-butenyl;

(d) (Lower)alkoxy includes C_1–C_6 alkoxy radicals, the alkyl portion of such radicals being defined as in (b) above. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, n-pentyloxy, isopentyloxy, n-hexyloxy, etc.;

(e) —O—(Lower)alkenyl groups include radicals in which the alkenyl portion is as defined above in (c), e.g. vinyloxy, allyloxy or isopropenyloxy;

(f) $-O-(CH_2)_m-CH(CH_2)_n$ includes cyclo(lower)-alkyloxy and cyclo(lower)alkyl-(C_1–C_6)alkyloxy groups in which the cycloalkyl ring contains from 3 to 8 carbon atoms, preferably 3–6 carbon atoms. Examples of such groups are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, cyclopropylmethyloxy, cyclopropylethyloxy, cyclobutylmethyloxy, cyclobutylethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cyclohexylethyloxy and cyclohexylpropyloxy;

(g) $-O-CH_2(CH_2)_xO(CH_2)_yCH_3$ includes radicals such as $-OCH_2OCH_3$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2OCH_2CH_3$, $-OCH_2OCH_2CH_3$ and $-OCH_2CH_2CH_2OCH_2CH_3$;

(h) (lower)alkylthio includes C_1–C_6 alkylthio radicals in which the alkyl portion is as defined above in (b). Examples of such groups are methylthio, ethylthio, n-propylthio and n-butylthio;

(i) (Lower)alkylamino includes C_1–C_6 alkylamino radicals in which alkyl is as defined in (b). Examples of such groups as methylamino, ethylamino, propylamino and butylamino;

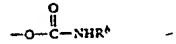
(j) Di(lower)alkylamino includes di C_1–C_6 alkylamino radicals in which alkyl is as defined above in (b). Examples of such groups are dimethylamino and diethylamino;

(k) —CO—(Lower)alkyl includes ester radicals in which the alkyl moiety is as defined above in (b), e.g. carbomethoxy, carbethoxy, carbopropoxy and carbobutoxy;

(l) $-O(CH_2)_aCO_2R^a$ represents radicals such as $-OCH_2CO_2H$, $-OCH_2CH_2CO_2H$, $-OCH_2CH_2CH_2CO_2H$, $-OCH_2CO_2CH_3$, $-OCH_2CO_2C_2H_5$, $-OCH_2CH_2CO_2CH_3$ and $-OCH_2CH_2CO_2C_2H_5$;

(m) $-N(CH_2)_r$ includes pyrrolidino and piperidino;

(n)

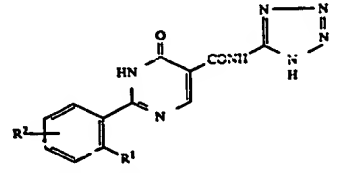


includes (lower)alkyl carbamoyloxy radicals in which the (lower)alkyl portion is as defined above in (b). Examples of such substituents include —O-CONHCH$_3$, —OCONHC$_2$H$_5$ and —O-CONHC$_3$H$_7$; and

(o) —O—(Lower)alkynyl includes groups in which the alkynyl moiety is a straight or branched unsaturated aliphatic hydrocarbon radical containing one triple bond and having from 2 to 6 carbon atoms inclusive, e.g. ethynyloxy, propargyloxy, butynyloxy, pentynyloxy or hexynyloxy.

A preferred embodiment of the present invention comprises the compounds of formula I as defined above wherein R^1, R^2 and R^3 are each independently selected from hydrogen, (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)-alkynyl, $-O-(CH_2)-CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, $-OCH_2C_6H_5$, halogen, CF_3, (lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, carboxy and (lower)alkylthio. Within this group of compounds, a more preferred embodiment comprises those compounds wherein R^1, R^2 and R^3 are each independently selected from hydrogen, (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, $-O-(CH_2)_m-CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7 and $-OCH_2C_6H_5$.

A more preferred embodiment of the present invention comprises the compounds of the formula

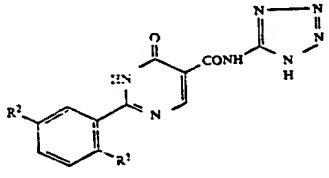


wherein R^1 and R^2 which may be the same or different are as defined above in connection with the compounds of general formula I, and the pharmaceutically acceptable salts thereof, with the proviso that when both R^1 and R^2 are tertiary alkyl or tertiary alkoxy groups, they are located on non-adjacent positions.

A preferred subgroup within the compounds defined by formula I' comprises the compounds wherein R^1 and R^2 are each independently selected from hydrogen, (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—CH(CH$_2$)$_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, —$OCH_2C_6H_5$, halogen, CF_3, (lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, carboxy and (lower)alkylthio. Within this subgroup, the preferred compounds are those in which R^1 and R^2 are each independently selected from hydrogen, (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—CH(CH$_2$)$_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7 and —$OCH_2C_6H_5$. The most preferred compounds within this latter group are those in which R^1 is a non-hydrogen substituent.

A most preferred subgroup within the compounds defined by formula I' comprises the compounds wherein R^1 is (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—CH(CH$_2$)$_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7 or —$OCH_2C_6H_5$ and R^2 is hydrogen, (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—CH(CH$_2$)$_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, —$OCH_2C_6H_5$, amino, di(lower)alkylamino or (lower)alkylthio.

Another more preferred embodiment of the present invention comprises the compounds of the formula



I''

wherein R^1 and R^2 which may be the same or different are as defined above in connection with the compounds of general formula I, and the pharmaceutically acceptable salts thereof.

A preferred subgroup within the compounds defined by formula I'' comprises the compounds wherein R^1 and R^2 are each independently selected from hydrogen, (lower)-alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—CH(CH$_2$)$_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, —$OCH_2C_6H_5$, halogen, CF_3, (lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, carboxy and (lower)alkylthio. Within this subgroup, the preferred compounds are those in which R^1 and R^2 are each independently selected from hydrogen, (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—CH(CH$_2$)$_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7 and —$OCH_2C_6H_5$. The most preferred compounds within this latter group are those in which R^1 is a nonhydrogen substituent.

A most preferred subgroup within the compounds defined by formula I'' comprises the compounds wherein R^1 is (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—CH(CH$_2$)$_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7 or —$OCH_2C_6H_5$ and R^2 is hydrogen, (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)-alkynyl, —O—$(CH_2)_m$—CH(CH$_2$)$_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, —$OCH_2C_6H_5$, amino, di(lower)alkylamino or (lower)alkylthio.

Other most preferred subgroups within the compounds defined by formula I'' are as follows:

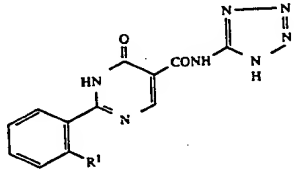
(a) compounds where R^1 is (lower)alkoxy, most preferably methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or t-butoxy;

(b) compounds where R^1 is —O—(lower)alkenyl, most preferably allyloxy;

(c) compounds where R^1 is —O—$(CH_2)_m$—CH(CH$_2$)$_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, most preferably cyclopropylmethoxy; and

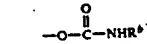
(d) compounds where R^1 is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, allyloxy or cyclopropylmethoxy and R^2 is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, allyloxy, cyclopropylmethoxy, amino or dimethylamino.

Another more preferred embodiment of the present invention comprises the compounds of the formula

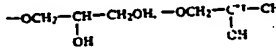


I'''

wherein R^1 is hydrogen, halogen, (lower)alkyl, (lower)-alkenyl, (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)-alkynyl, —O—$(CH_2)_m$—CH(CH$_2$)$_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, —$OCH_2(CH_2)_xO(CH_2)_yCH_3$ in which x is 0 or an integer from 1 to 6 and y is 0 or an integer from 1 to 6, CF_3, —OCF_3, —OCH_2CF_3, hydroxy, (lower)alkylthio, amino, nitro, —N(CH$_2$)$_r$ in which r is 4 or 5, (lower)alkylamino, di(lower)alkylamino, carboxyl, —CO_2—(lower)alkyl, —$O(CH_2)_uCO_2R^a$ in which u is an integer from 1 to 6 and R^a is hydrogen or (lower)alkyl, R^c—CO— in which R^c is (lower)alkyl, R^c—CONH— in which R^c is (lower)-alkyl, R^c—COO— in which R^c is (lower)alkyl,



in which R^b is (lower)alkyl, —$O(CH_2)_kOH$ in which k is an integer from 2 to 6,



or —$OCH_2C_6H_5$, or a pharmaceutically acceptable salt thereof.

A preferred subgroup within the compounds defined by formula I''' comprises the compounds wherein R^1 is hydrogen, (lower)alkoxy, —O—(lower)alkenyl,

—O—(lower)-alkynyl, —O—$(CH_2)_m$—CH$((CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, —$OCH_2C_6H_5$, halogen, CF_3, (lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, carboxy or (lower)alkylthio. Within this subgroup, the preferred compounds are those in which R^1 is (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)-alkynyl, —O—$(CH_2)_m$—CH$((CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7 or —$OCH_2C_6H_5$.

Other preferred subgroups within the compounds defined by formula I''' are as follows:

(a) compounds where R^1 is (lower)alkoxy, most preferably methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or t-butoxy;

(b) compounds where R^1 is —O—(lower)alkenyl, most preferably allyloxy;

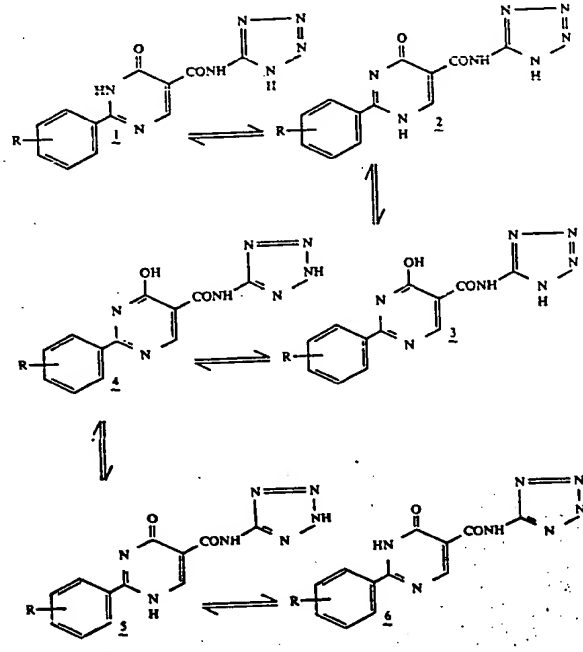
(c) compounds where R^1 is —O—$(CH_2)_m$—CH$((CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, most preferably cyclopropylmethoxy;

(d) compounds where R^1 is —O—(lower)alkynyl; and

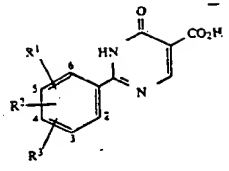
(e) compounds where R^1 is —$OCH_2C_6H_5$.

The term "pharmaceutically acceptable salt" as used herein is intended to include non-toxic cationic salts such as the alkali metal salts, e.g. sodium and potassium, alkaline earth metal salts such as calcium, magnesium or barium, aluminum salts, ammonium salts, and salts with organic bases, e.g. amines such as triethylamine, n-propylamine, tri-n-butylamine, piperidine, ethanolamine, diethanolamine, triethanolamine, diethylaminoethylamine, ethylenediamine, N,N'-dibenzylethylenediamine, benzylamine, tris(hydroxymethyl)aminomethane or pyrrolidine. Salt formation is accomplished by reacting the appropriate pyrimidine-5-N-(1H-tetrazol-5-yl)carboxamide with a substantially equimolar amount of the appropriate base in an aqueous solution or in a suitable organic solvent such as methanol or ethanol. The salts are recovered by standard methods such as filtration if they are insoluble in the reaction medium, or if they are soluble in the medium, by evaporation or by precipitation by addition of a non-solvent for the salt.

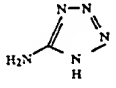
Those skilled in the art will appreciate that the compounds represented by structural formulae I–I''' are capable of also existing in the tautomeric forms shown below. All of the forms may be present to a greater or lesser degree and may co-exist in a dynamic equilibrium mixture. While all of the various tautomeric forms are included within the scope of the present invention, the form represented by formula 1 below has been arbitrarily used herein for the sake of convenience to describe the present compounds.



The compounds of formula I may be prepared by coupling of the appropriate pyrimidine-5-carboxylic acid of the formula

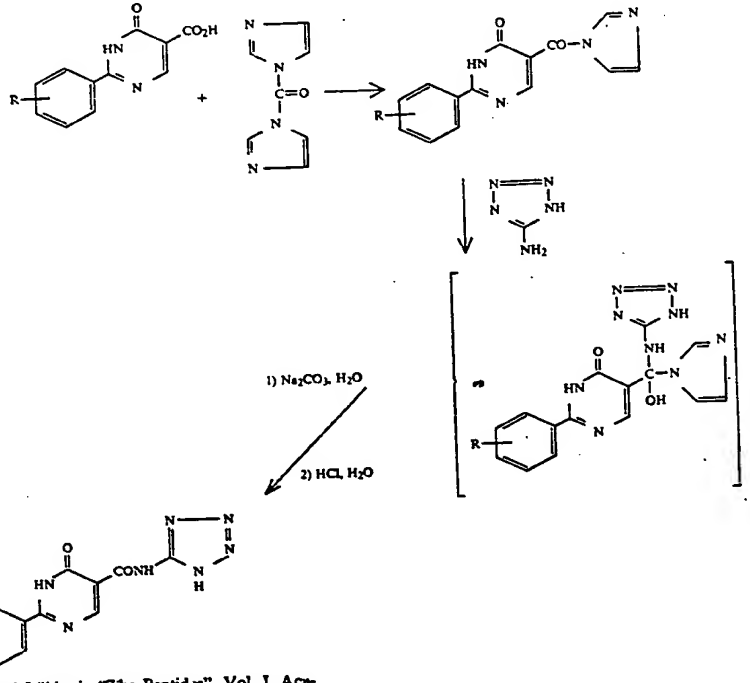


wherein R^1, R^2 and R^3 are as defined above with 5-a nitrotetrazole of the formula



The coupling of the acid II with the amino-tetrazole III may be accomplished with the aid of a variety of reagents commonly used, for example, in peptide synthesis. Examples of these reagents are described by Schröder and Lübke in "The Peptides", Vol. I, Academic Press, N.Y., 1965, pp. 77–128. The general principle of the synthesis is activation of the carboxyl group by either formation, for example, of the corresponding acid azide, acid halide (preferably the acid chloride), mixed anhydride (e.g. with carbonic acid monoesters), activated ester (e.g. p-nitrophenyl), or heterocyclic amide (e.g. imidazolide), or by treatment with a carbodiimide (e.g. N,N'-dicyclohexylcarbodiimide). Treatment of the activated carboxyl group with 5-aminotetrazole results in amide formation. The coupling reaction is carried out in a reaction-inert solvent system. The variety of coupling reagents which can be used allows a wide choice of solvents. Representative solvents are N,N-dimethylformamide, tetrahydrofuran, dioxane, methylene chloride, nitromethane, acetonitrile, dimethylsulfoxide, N,N-dimethylacetamide and hexamethylphosphoramide. Reaction times and temperatures are not critical. For good yields of products within a reasonable length of time, convenient temperatures are in the range of about 20°–100° C. for both steps, i.e. reaction of the acid with the coupling agent the reaction of the activated intermediate with the 5-aminotetrazole. The coupling reaction may be carried out either in stepwise fashion, i.e. by isolating the activated intermediate before addition of the 5-aminotetrazole, or by adding all reactants at once.

A preferred method of coupling utilizes N,N'-carbonyldiimidazole and is illustrated by the following scheme:



This reaction scheme may be carried out using the reaction-inert solvents mentioned above in both the imidazolide formation step and the step in which the imidazolide (either in situ or isolated) is reacted with the

aminotetrazole. Preferred solvents are tetrahydrofuran and N,N-dimethylformamide. The reaction temperature is not critical, but a convenient temperature range for both steps has been found to be about 20°–100° C.

The pyrimidine-5-carboxylic acids of formula II may be prepared as described in U.S. Pat. No. 4,031,093 or by hydrolysis of the pyrimidine-5-carboxylate esters disclosed in U.S. Pat. No. 4,082,751. The 5-aminotetrazole starting material is commercially available.

In preparing compounds of formula I which contain free hydroxy, amino or carboxyl groups, it is of course understood that such groups will be protected by conventional protecting groups during the coupling reaction of II with III. The protecting group(s) may then be removed by methods known per se to give the desired end-products having the unprotected substituent groups. Amino-substituted compounds may be prepared from the corresponding nitro-substituted product by catalytic hydrogenation. In preparing compounds of formula I where R^1, R^2 or R^3 are (lower)alkylamino or di(lower)alkylamino, the corresponding amino-substituted compound may first be prepared and then alkylated. Alternatively, the dialkylamino-substituted compounds can be prepared directly from the appropriate starting material of formula II.

In another aspect, the present invention provides a method of inhibiting or preventing the symptoms of an allergic reaction such as bronchial asthma, allergic rhinitis, urticaria, allergic conjunctivitis, systemic anaphylaxis, atopic dermatitis and food allergy in a mammal susceptible to such a reaction which comprises administering to said mammal a prophylactically effective dose of a compound of formula I or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may be administered either as individual therapeutic agents or as mixtures with other therapeutic agents. They may be administered alone but are generally administered in the form of pharmaceutical compositions, i.e. mixtures of the active agents with suitable pharmaceutical carriers or diluents. Examples of such compositions include tablets, lozenges, capsules, powders, aerosol sprays, aqueous or oily suspensions, syrups, elixirs and aqueous solutions. The compounds are preferably administered orally, but may also be administered by inhalation, injection, instillation or by implantation for controlled drug release from a solid carrier reservoir.

The nature of the pharmaceutical composition and the pharmaceutical carrier or diluent will, of course, depend on the desired route of administration. For example, oral compositions may be in the form of tablets or capsules and may contain conventional excipients such as binding agents (e.g. syrup, acacia, gelatin, sorbitol, tragacanth or polyvinylpyrrolidone), fillers (e.g. lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine), lubricants (e.g. magnesium stearate, talc, polyethylene glycol, or silica), disintegrants (e.g. starch) or wetting agents (e.g. sodium lauryl sulfate). Oral liquid preparations may be in the form of aqueous or oily suspensions, solutions, emulsions, syrups, elixirs, etc. or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, flavoring agents, diluents or emulsifying agents. For parenteral administration, inhalation or instillation, solutions or suspensions of a compound of formula I with conventional pharmaceutical vehicles may be employed, e.g. as an aerosol spray for inhalation, as an aqueous solution for intravenous injection or instillation or as an oily suspension for intramuscular injection. The compounds may also be administered by means of inhalers or other devices which permit the active compounds in the form of dry powders to come into direct contact with the lungs.

The compounds of the present invention or pharmaceutical compositions thereof may be administered to human allergic patients in single oral doses of approximately 0.5—500 mg. of active ingredient and multiple oral doses totalling up to about 1000 mg./day of active ingredient. When administered by inhalation or instillation, lower doses are generally given, i.e. on the order of about 0.1 of the normal oral dosage for the particular compound in question. These values are illustrative only, however, and the physician of course will ultimately determine the dosage most suitable for a particular patient on the basis of factors such as age, weight, severity of the symptoms and the particular agent to be administered.

The in vivo animal model studies described below indicate that the compounds of formula I are highly potent antiallergy agents.

BIOLOGICAL ACTIVITY DATA

The reagin-mediated rat Passive Cutaneous Anaphylaxis (PCA) screening test used to evaluate the present compounds is generally regarded as one of the best animal models for use in predicting the antiallergy activity of test compounds in man. This screen provides a measure of the effectiveness of test compounds in either inhibiting the release or antagonizing the action of mediator arising from the interaction of reaginic antibodies with specific antigen, mediators which are causative factors in allergic disorders. The details of the test are fully described in U.S. Pat. No. 4,031,093.

The test compounds were solubilized in aqueous sodium bicarbonate and administered intravenously (i.v.) or per os (p.o.) either one or ten minutes, respectively, prior to antigen callenge. Disodium cromoglycate (DSCG), solubilized in saline, was administered i.v. at the time of challenge and p.o. 30 minutes prior to challenge. Test results were recorded in terms of the ID_{50} value, i.e. the dose of compound that inhibits 50% of the response. To illustrate the relative potency of the present compounds, the compound of Example 1 in the rat PCA test was found to have an ID_{50} of ~0.051 mg./kg. (i.v.) and ~0.56 mg./kg. (p.o.) as compared to 0.6 mg./kg. (i.v.) and >>30 mg./kg. (p.o.) for DSCG.

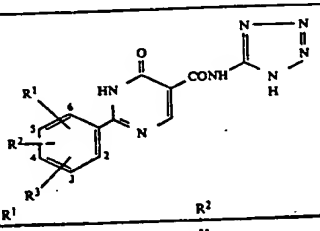
The following examples are provided solely for the purpose of illustrating preparation of the compounds of the present invention and are not to be construed as limitations of the invention. All temperatures referred to below are in degrees Celsius. The compounds shown below in Examples 1 and 2 have the general structural formula

-continued

Table A	Table B
5-carboxylic acid	5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(2-ethylthiophenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(2-ethylthiophenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(2-methylthiophenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(2-methylthiophenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(2-nitrophenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(2-nitrophenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(2-aminophenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(2-aminophenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(4-methylphenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(4-methylphenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(3-methylphenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(3-methylphenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(3-chlorophenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(3-chlorophenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(4-hydroxyphenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(4-hydroxyphenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(3,4-dimethoxyphenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(3,4-dimethoxyphenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(3,4,5-trimethoxyphenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(3,4,5-trimethoxyphenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(3-acetamidophenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(3-acetamidophenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(2-acetamidophenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(2-acetamidophenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(4-dimethylaminophenyl)-pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(4-dimethylaminophenyl)-pyrimidine-5-N-(1H-tetrazol-5-yl)carboxamide
1,6-dihydro-6-oxo-2-(3,5-dibromophenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(3,5-dibromophenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(4-butylthiophenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(4-butylthiophenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(4-methylthiophenyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(4-methylthiophenyl)pyrimidine-5-N-(1H-tetrazol-5-yl)-carboxamide
1,6-dihydro-6-oxo-2-(3-amino-2-n-propoxyphenyl)-pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(5-amino-2-n-propoxyphenyl)-pyrimidine-5-N-(1H-tetrazol-5-yl)carboxamide
1,6-dihydro-6-oxo-2-(5-dimethylamino-2-n-propoxy-pheyl)pyrimidine-5-carboxylic acid	1,6-dihydro-6-oxo-2-(5-dimethylamino-2-n-propoxy-pheyl)pyrimidine-5-N-(1H-tetrazol-5-yl)carboxamide

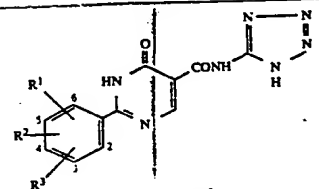
EXAMPLE 3

Following the general procedure of Example 1, the following compounds may be prepared by use of the appropriate pyrimidine-5-carboxylic acid starting material.



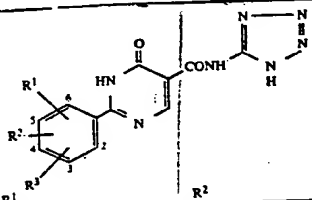
R^1	R^2	R^3
H	H	H
2-CH_3	H	H
2-C_2H_5	H	H
2-C_3H_7	H	H
2-$CH_2CH{=}CH_2$	H	H
2-$CH{=}CH_2$	H	H
2-cyclopropyloxy	H	H
2-cyclobutyloxy	H	H
2-OCH_2OCH_3	H	H
2-$OCH_2CH_2OCH_3$	H	H
2-CF_3	H	H
2-OCF_3	H	H
2-OCH_2CF_3	H	H

-continued



R^1	R^2	R^3
	H	H
2-$NHCH_3$	H	H
2-NHC_2H_5	H	H
2-$N(CH_3)_2$	H	H
2-COOH	H	H
2-$COOCH_3$	H	H
2-$COOC_2H_5$	H	H
2-OCH_2CO_2H	H	H
2-$OCH_2CO_2CH_3$	H	H
2-$OCONHCH_3$	H	H
2-$OCCH_3$ (O)	H	H
2-OCC_2H_5 (O)	H	H
2-$OCCH_3$ (O)	H	H
2-OCH_2CH_2OH	H	H
2-$OCH_2CH(OH)CH_2OH$	H	H
2-$OCH_2CH(OH)CH_2OCH_3$	H	H
2-$OCH_2CH_2CH_2OH$	H	H
2-$OCH{=}CH_2$	H	H
2-$OC(CH_3)_3$	H	H
2-$OC{\equiv}CCH_3$	H	H
2-$OCH_2CH_2C{\equiv}CH$	H	H
2-$OC{\equiv}CH$	H	H
2-F	5-F	H
2-cyclopropylethoxy	H	H
2-cyclobutylmethoxy	H	H
2-cyclopentyloxy H	H	
2-O-n-C_3H_7	5-Cl	H
"	5-F	H
"	5-CH_3	H
"	5-C_2H_5	H
"	5-$CH_2CH{=}CH_2$	H
"	5-$CH{=}CH_2$	H
"	5-OC_2H_5	H
"	5-O-n-C_3H_7	H
"	5-$OCH(CH_3)_2$	H
"	5-$OCH_2CH{=}CH_2$	H
"	5-$OCH_2CH_2OCH_3$	H
"	5-CF_3	H
"	5-OCF_3	H
"	5-OCH_2CF_3	H
"	5-OH	H
"	5-SCH_3	H
"	5-$NHCH_3$	H
"	5-N ()	H

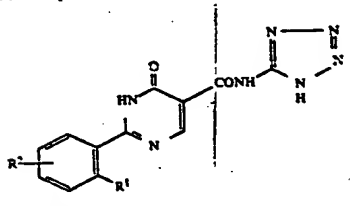
-continued



R^1	R^2	R^3
"	5-N	H
"	$5\text{-NHC}_2\text{H}_5$	H
"	5-COOH	H
"	$5\text{-CO}_2\text{CH}_3$	H
"	$5\text{-CO}_2\text{C}_2\text{H}_5$	H
"	$5\text{-OCH}_2\text{CO}_2\text{H}$	H
"	$5\text{-OCH}_2\text{CO}_2\text{CH}_3$	H
"	5-O-CONHCH_3	H
"	5-CCH3 (O)	H
"	5-C-C2H5 (O)	H
"	5-NHCCH3 (O)	H
"	5-O-CCH3 (O)	H
"	$5\text{-OCH}_2\text{CH}_2\text{OH}$	H
"	$5\text{-OCH}_2\text{-CHCH}_2\text{OH}$ (OH)	H
"	$5\text{-OCH}_2\text{-CH-CH}_2\text{OCH}_3$ (OH)	
"	$5\text{-OCH}_2\text{C}_6\text{H}_5$	H
$2\text{-O-CH(CH}_3)_2$	5-OCH3	H
"	$5\text{-OC}_2\text{H}_5$	H
"	5-O-n-C3H7	H
"	$5\text{-OCH(CH}_3)_2$	H
"	$5\text{-OCH}_2\text{CH=CH}_2$	H
"	5-CF_3	H
$2\text{-OC}_2\text{H}_5$	$5\text{-OC}_2\text{H}_5$	H
"	5-O-n-C3H7	H
"	$5\text{-OCH(CH}_3)_2$	H
$2\text{-O-n-C}_4\text{H}_9$	$5\text{-OC}_2\text{H}_5$	H
"	5-O-n-C3H7	H
"	$5\text{-OCH(CH}_3)_2$	H
2-OCH_3	4-OCH3	6-OCH3

I claim:

1. A compound having the formula



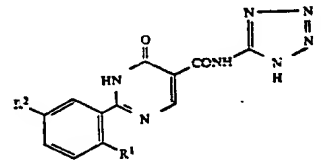
wherein R^1 and R^2 which may be the same or different are each hydrogen, halogen, (lower)alkyl, (lower)-alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, $-O-(CH_2)_m-CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, CF_3, hydroxy, (lower)alkylthio, amino, (lower)alkylamino, di(-lower)-alkylamino, carboxyl, or $-OCH_2C_6H_5$, or a pharmaceutically acceptable salt thereof, with the proviso that when R^1 and R^2 are tertiary alkyl or tertiary alkoxy they are located on non-adjcent positions.

2. A compound of claim 1 wherein R^1 and R^2 are each independently selected from hydrogen, (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, $-O-(CH_2)_m-CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7 or $-OCH_2C_6H_5$.

3. A compound of claim 1 wherein R^1 is (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, $-O-(CH_2)_m-CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7 or $-OCH_2C_6H_5$ and R^2 is hydrogen, (lower)alkoxy,

—O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—$CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, —$OCH_2C_6H_5$, amino, di(lower)alkylamino or (lower-)alkylthio.

4. A compound having the formula



wherein R^1 and R^2 which may be the same or different are each hydrogen, halogen, (lower)alkyl, (lower)-alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—$CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, CF_3, hydroxy, (lower)alkylthio, amino, (lower)alkylamino, di(-lower)-alkylamino- carboxyl, or —$OCH_2C_6H_5$, or a pharmaceutically acceptable salt thereof.

5. A compound of claim 4 wherein R^1 and R^2 are each independently selected from hydrogen, (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—$CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7 or —$OCH_2C_6H_5$.

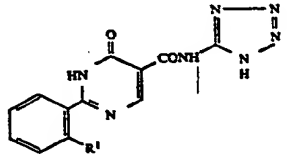
6. A compound of claim 4 wherein R^1 is (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—$CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7 or —$OCH_2C_6H_5$ and R^2 is hydrogen, (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—$CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, —$OCH_2C_6H_5$, amino di(lower)alkylamino or (lower)alkylthio.

7. A compound of claim 4 wherein R^1 is n-propoxy and R^2 is methoxy.

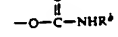
8. a compound of claim 4 wherein R^1 is n-propoxy and R^2 is amino.

9. A compound of claim 4 wherein R^1 is n-propoxy and R^2 is dimethylamino.

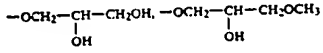
10. A compound having the formula



wherein R^1 is hydrogen, halogen, (lower)alkyl, (lower-)alkenyl, (lower)alkoxy, —O—(lower)alkenyl, —O—(-lower)alkynyl, —O—$(CH_2)_m$—$CH(CH_2)_n$ is which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, —$OCH_2(CH_2)_xO(CH_2)_yCH_3$ in which x is 0 or an integer from 1 to 6 and y is 0 or an integer from 1 to 6, CF_3, —OCF_3, —$OCH_2C_6H_5$, hydroxy, (lower)alkylthio, amino, nitro, —$N(CH_2)_r$ in which r is 4 or 5, (lower)alkylamino, di-(lower)alkylamino, carboxyl, —CO_2—(-lower)alkyl, —$O(CH_2)_uCO_2R^a$ in which u is an integer from 1 to 6 and R^a is hydrogen or (lower)alkyl, R^c—CO— in which R^c is (lower)alkyl, R^c—CONH— in which R^c is (lower)alkyl, R^c—COO— in which R^c is (lower)-alkyl,



—in which R^b is (lower)alkyl, —$(CH_2)_kOH$ in which k is an integer from 2 to 6,



or —$OCH_2C_6H_5$, or a pharmaceutically acceptable salt thereof.

11. A compound of claim 10 wherein R^1 is hydrogen, (lower)-alkoxy, —O—(lower)alkenyl, —O—(lower-)alkynyl, —O—$(CH_2)_m$—$CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7, —$OCH_2C_6H_5$, halogen, CF_3, (lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, carboxy or (lower) alkylthio.

12. A compound of claim 10 wherein R^1 is (lower)alkoxy, —O—(lower)alkenyl, —O—(lower)alkynyl, —O—$(CH_2)_m$—$CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7 or —$OCH_2C_6H_5$.

13. A compound of claim 10 wherein R^1 is (lower)alkoxy.

14. A compound of claim 10 wherein R^1 is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or t-butoxy.

15. The compound of claim 10 wherein R^1 is methoxy.

16. The compound ot claim 10 wheren R^1 is ethoxy.

17. The compound of claim 10 wherein R^1 is n-propoxy.

18. The compound of claim 10 wherein R^1 is isopropoxy.

19. The compound of claim 10 wherein R^1 is n-butoxy.

20. The compound of claim 10 wherein R^1 is sec-butoxy.

21. The compound of claim 10 wherein R^1 is t-butoxy.

22. A compound of claim 10 where R^1 is —O—(-lower)-alkenyl.

23. The compound of claim 10 wherein R^1 is allyloxy.

24. A compound of claim 10 wherein R^1 is —O—(-lower)-alkynyl.

25. A compound of claim 10 wherein R^1 is —O—$(CH_2)_m$—$CH(CH_2)_n$ in which m is 0 or an integer from 1 to 6 and n is an integer from 2 to 7.

26. The compound of claim 10 wherein R^1 is cyclopropylmethoxyl.

27. The compound of claim 10 wherein R^1 is —$OCH_2C_6H_5$.

* * * * *